

4-AZA-1,2-DITHIANE-5-ONE AND RELATED SYSTEMS;  
SYNTHESIS, STRUCTURE DETERMINATIONS AND STABILITY

Zev Lidert

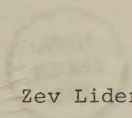
Organisk kemi 1, Kemicentrum

Lunds Universitet

Lund 1980



4-AZA-1,2-DITHIANE-5-ONE AND RELATED SYSTEMS;  
SYNTHESIS, STRUCTURE DETERMINATIONS AND STABILITY



Zev Lidert

Organisk kemi 1, Kemicentrum

Lunds Universitet

Lund 1980



This review is a summary of results published in the following papers, which will be referred to as I...VI.

- I. S. Gronowitz and Z. Lidert  
A Convenient Synthesis of N-Substituted N-chloromethyl Carboxamides.  
Synthesis 1979, 810.
- II. Z. Lidert and S. Gronowitz  
Preparation of 2-Substituted Derivatives of  
Some  $\alpha$ -Amino Acids.  
Synthesis 1980, 322.
- III. I. Cynkier, S. Gronowitz, H. Hope and Z. Lidert  
Regiospecific Dimerization Leading to a 14-Membered Heterocyclic Ring. Synthesis and X-Ray Structure.  
J. Org. Chem. 44 (1979) 4699.
- IV. S. Gronowitz and Z. Lidert  
Conformational Effects on Disulphide Formation  
from Unsymmetrical Dithiols.  
Chemica Scripta, in press.
- V. Z. Lidert and S. Gronowitz  
Further Studies on Disulphide Formation  
from Unsymmetrical Dithiols.  
Chemica Scripta, in press.
- VI. Z. Lidert  
Conformation and Barrier to Inversion of a 12-Membered Heterocycle Containing Two Disulfide Bonds.  
Organic Magnetic Resonance, submitted for publication.





# CONTENTS

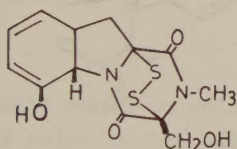
|                                                                                     | Page |
|-------------------------------------------------------------------------------------|------|
| 1. INTRODUCTION                                                                     | 7    |
| 2. SYNTHESIS OF N-(ACETYLTHIO)METHYL-2-(ACETYLTHIO)ACETAMIDES                       | 11   |
| 2.1. N-Halomethyl-haloacetamides via N-hydroxymethyl-haloacetamide                  | 11   |
| 2.2. N-Halomethyl-haloacetamides from hexahydrotriazines                            | 12   |
| 2.3. N-Halomethyl-haloacetamides from imines                                        | 14   |
| 2.4. N-Halomethyl-haloacetamides from $\alpha$ -amino acids                         | 16   |
| 3. 4-AZA-1,2-DITHIANE-5-ONES AND THE RELATED 12-MEMBERED HETEROCYCLES               | 19   |
| 3.1. Synthesis                                                                      | 19   |
| 3.1.1. Synthesis of N-thiomethyl-2-thioacetamides                                   | 19   |
| 3.1.2. Oxidations of N-thiomethyl-2-thioacetamides                                  | 20   |
| 3.1.3. Structure determinations of the so formed disulfides                         | 21   |
| 3.1.4. Mechanism of oxidations                                                      | 24   |
| 3.2. Stability of the 4-aza-1,2-dithiane-5-one system                               | 26   |
| 3.3. Stability of 12-membered ring systems related to 4-aza-1,2-dithiane-5-ones     | 28   |
| 4. REGIOSPECIFIC REACTION OF ANISALDEHYDE WITH N-THIOMETHYL-THIOGLYCOLIC ACID AMIDE | 30   |
| 5. ANTIVIRAL ACTIVITY OF 4-AZA-1,2-DITHIANE-5-ONES AND CONCLUSIONS                  | 32   |
| REFERENCES                                                                          | 33   |



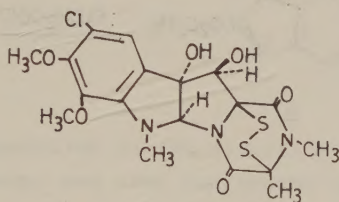


## 1. INTRODUCTION

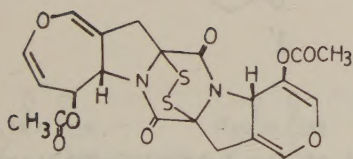
Naturally occurring compounds such as gliotoxin (1a), sporidesmin (1b) and acetylaranotin (1c), containing the epidithiopiperazinedione nucleus, have received growing attention during the last decade due to their antiviral properties.<sup>1</sup> A general approach to this class was presented by Kishi et al.,<sup>2</sup> and additionally, the easily prepared, simple analogues 2,<sup>3,4</sup> for instance N,N'-dimethyl-epidithiopiperazinedione<sup>4</sup> (2:  $R_1 = \text{CH}_3$ ,  $R_2 = R_3 = \text{H}$ ), were shown to possess high activity, inhibiting viral RNA synthesis at low concentrations.



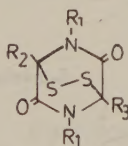
1a



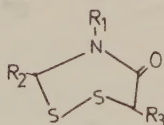
1b



1c



2

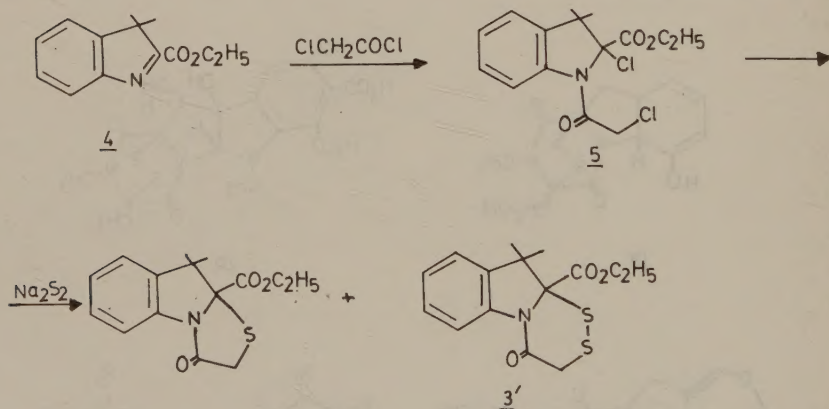


3

An interesting question arises, as to whether the epidithiopiperazinedione moiety is needed in its entirety for the antiviral activity of 1a-c and 2 or if there exists a part of it capable of inhibiting viral RNA synthesis. Such a structure would have to contain the disulfide function, which was shown

to be essential for the antiviral activity of gliotoxin (1a) and related compounds.<sup>1</sup> Thus, 4-aza-1,2-dithiane-5-ones 3, formally derived from 2 by removal of one of the amido functions, seemed to be interesting subjects for such a study.

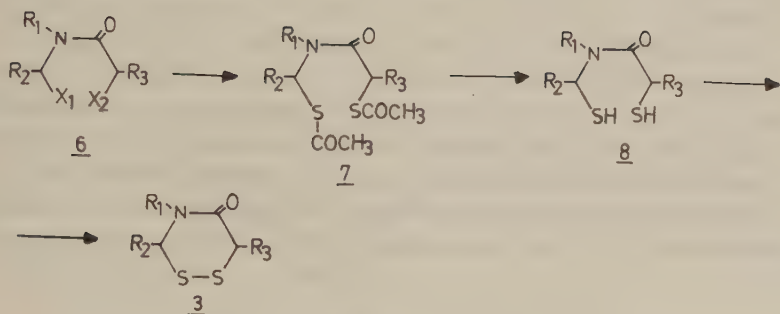
The 4-aza-1,2-dithiane structure was, prior to our investigation, reported once in the literature, in connection with attempts to synthesize a gliotoxin analogue.<sup>5</sup> Thus, starting from the indolenine derivative 4, N-chloroacetyl-2-chloroindolenine ester 5 was prepared by treatment with chloroacetyl chloride (Scheme 1). Using sodium disulfide, this compound was then converted to a mixture in which compound 3', containing the 4-aza-1,2-dithiane-5-one structure, was present.



Scheme 1

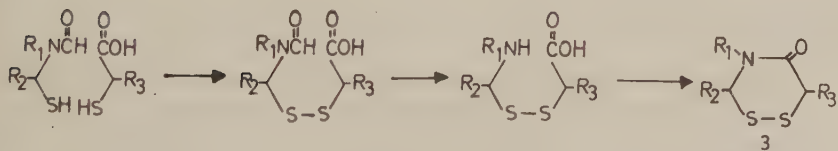
In this approach, the amide bond of the 4-aza-1,2-dithiane-5-one structure was prepared prior to the disulfide linkage.

Adopting a similar strategy, we decided to carry out the preparations of 4-aza-1,2-dithiane-5-ones 3 starting from N-halomethyl-haloacetamides 6. Conversion of 6 to the dithioacetates 7 followed by hydrolysis was expected to give the dithiols 8, which on oxidation were hoped to afford 4-aza-1,2-dithiane-5-ones 3 (Scheme 2).



Scheme 2

A synthetic route in which preparation of the disulfide linkage occurred prior to the amide group, was also considered but, since  $\alpha$ -aminodisulfides are known to be unstable,<sup>6</sup> this approach (Scheme 3) did not seem to be very promising.



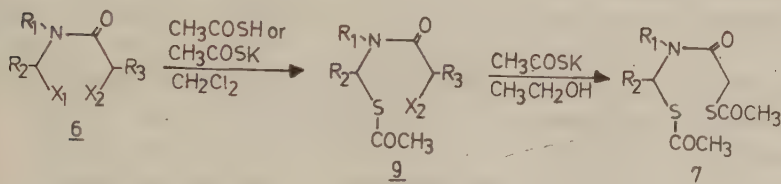
Scheme 3

Papers I, II and, to some extent, III deal with the synthesis of the dithioacetates 7. These compounds were prepared according to Scheme 2 via the generally valuable synthetic intermediates, N-chloromethyl-carboxamides 6.<sup>7</sup> Two new approaches to these intermediates are presented in Papers I and II.

Oxidation of the dithiols 8 is described in Papers IV and V and the stability of the 4-aza-1,2-dithiane-5-one system is also discussed in Paper V. Structure determination of a 12-membered heterocycle resulting from oxidation of N-phenyl-N-thiomethyl-2-(thio)acetamide is the subject of Paper VI.

## 2. SYNTHESIS OF N-(ACETYLTHIO)METHYL-2-(ACETYLTHIO)- ACETAMIDES

N-(Acetylthio)methyl-2-(acetylthio)acetamides 7 were easily obtained from the corresponding N-halomethyl-haloacetamides 6. Thus, treatment of crude 6 in methylene chloride with potassium thioacetate or thiolacetic acid yielded the monosubstituted products N-(acetylthio)methyl-haloacetamides 9, which, usually without isolation, were reacted with potassium thioacetate in ethanol to yield 7 (Scheme 4).

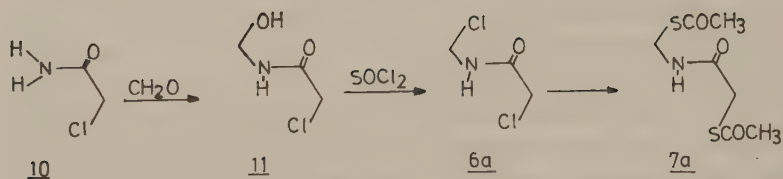


Scheme 4

N-Halomethyl carboxamides are extremely reactive synthetic intermediates, being widely used in many fields.<sup>7</sup>

### 2.1. N-Halomethyl-haloacetamides via N-hydroxy-haloacetamides

The precursor of N-(acetylthio)methyl-(acetylthio)acetamide (7a),<sup>III</sup> N-chloromethyl-chloroacetamide (6a), was easily obtained from N-hydroxymethyl-chloroacetamide 11 (Scheme 5) on reaction with thionyl chloride.<sup>8</sup> Compound 11 was itself prepared by condensation of chloroacetamide 10 with formaline, according to well-known procedure.<sup>7</sup>



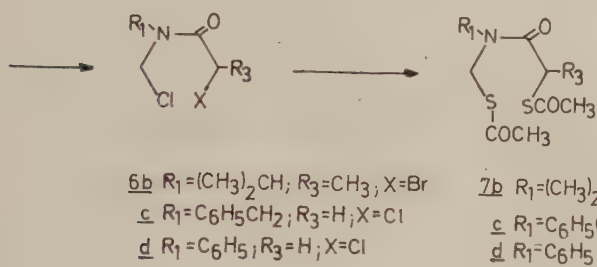
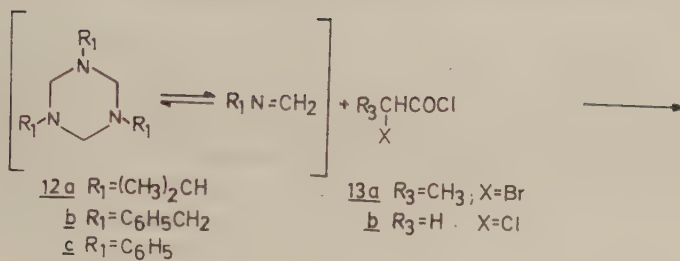
Scheme 5

A similar condensation was reported to take place when N-alkyl carboxamides were heated with paraformaldehyde in open systems at  $110^\circ\text{C}$  or in closed systems at  $140^\circ\text{C}$ .<sup>9</sup> However, no reaction was observed when these procedures were applied to N-benzyl or N-phenyl chloroacetamides, possibly due to the high melting points of these amides.<sup>1</sup> Thus, the traditional approach to N-alkyl-N-chloromethyl carboxamides via the corresponding N-hydroxymethyl derivatives<sup>9</sup> was not viable for this class of compounds, at least.

## 2.2. N-Halomethyl-haloacetamides from hexahydrotriazines

A more convenient and general approach than the traditional one (Section 2.1.) proved to be one based on the reaction of carboxylic acid chlorides with hexahydrotriazines 12 (Scheme 6).<sup>1</sup> The latter compounds are easily obtained by mixing simple aliphatic amines with formaldehyde.<sup>10</sup> By this method N-chloromethyl-N-i-propyl-2-bromopropanamide (6b), N-benzyl-N-chloromethyl-chloroacetamide (6c) and N-chloromethyl-N-phenyl-chloroacetamide (6d) were prepared and subsequently converted to the corresponding dithioacetates 7b-d (Scheme 6).<sup>1</sup>



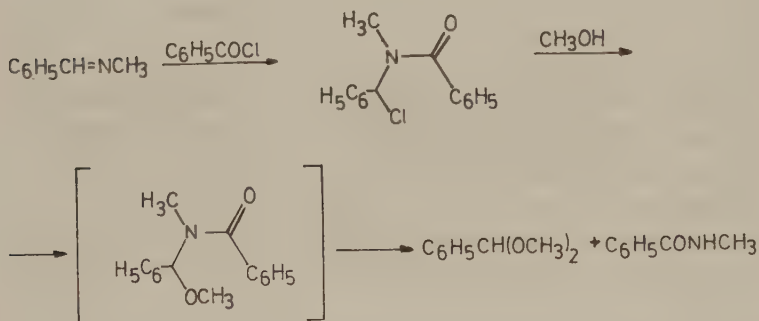


Scheme 6

The reaction of the hexahydrotriazines 12 with the acid chlorides 13 may in fact proceed via the monomeric imines present in equilibrium with the trimers 12 (Scheme 6). This is supported by the fact that the stable imines of formaldehyde and 2,6-disubstituted anilines react with acid chlorides to give the corresponding N-chloromethyl carboxamides.<sup>11</sup>

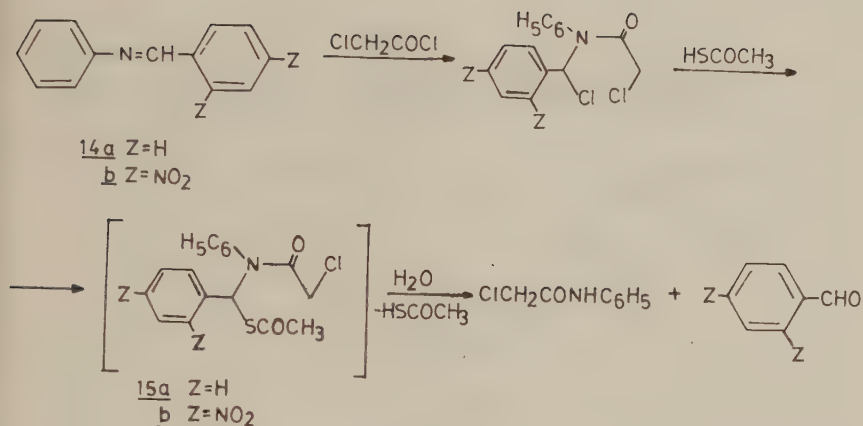
### 2.3. N-Halomethyl-haloacetamides from imines

N-(Aryl or alkyl)chloromethyl carboxamides have been prepared by the addition of acid chlorides to the azomethine bond of stable imines obtained from aromatic or aliphatic aldehydes.<sup>12,13</sup> These aldehydes or the corresponding acetals, are reobtained on treatment of the N-(aryl or alkyl)chloromethyl carboxamides with water or alcohol. The reaction proceeds via the unstable N-(aryl or alkyl)oxymethyl derivatives, as in the example below.<sup>12</sup>



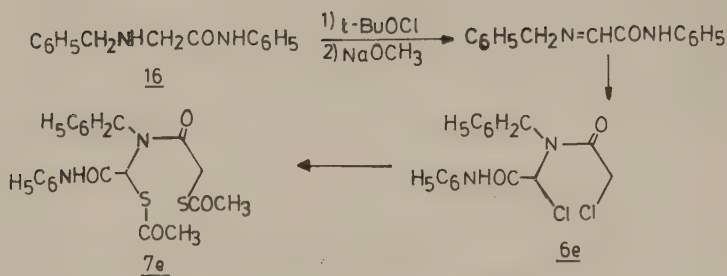
Scheme 7

In the light of the known instability of N-(aryl)alkoxymethyl carboxamides,<sup>12</sup> a failure to obtain thioacetates 15a and 15b from imines 14a and 14b<sup>29</sup> by treatment with chloroacetyl chloride and then thiolacetic acid (Scheme 8) could not be entirely unexpected.<sup>14</sup>



Scheme 8

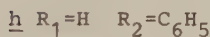
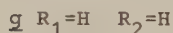
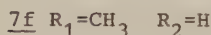
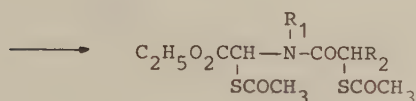
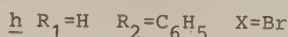
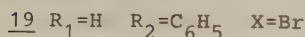
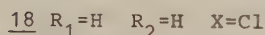
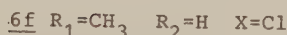
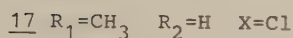
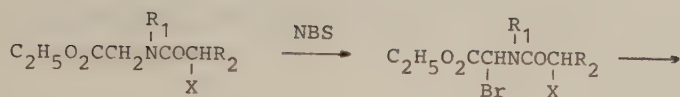
On the other hand, 2-acetylthio derivatives of  $\alpha$ -amino acids are known to be stable.<sup>15</sup> Indeed, N-(acetylthio)acetyl-N-benzyl-2-(acetylthio)glycine anilide (7e),<sup>II</sup> prepared from N-benzyl-glycine anilide (16)<sup>II</sup> via N-benzyl-N-chloroacetyl-2-chloroglycine anilide (6e) according to a known procedure<sup>16</sup> (Scheme 9), was found stable.



Scheme 9

#### 2.4. N-Halomethyl-N-haloacetamides from $\alpha$ -amino acids

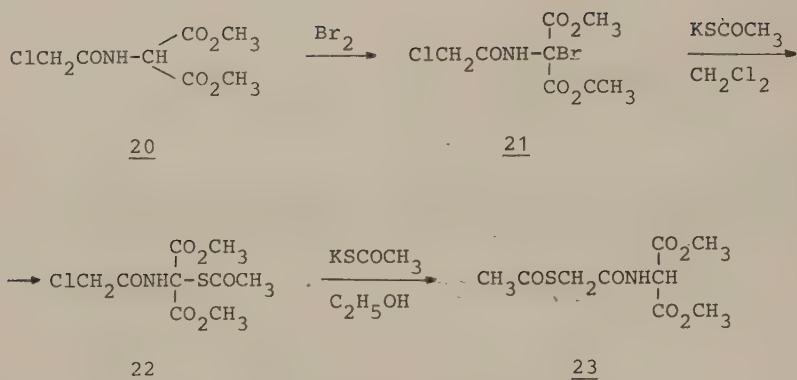
NBS bromination of N-acyl glycinate and sarcosinate was found to be a new, convenient approach to N-((alkoxycarbonyl)-bromomethyl)carboxamides.<sup>II</sup> Thus, N-chloroacetyl ethyl sarcosinate (**17**), N-chloroacetyl ethyl glycinate (**18**) and N-{2-(bromo)phenacetyl}ethyl glycinate **19** gave, on treatment with NBS, the 2-bromo derivatives **6f**, **6g** and **6h** which, after work-up with potassium thioacetate, yielded the corresponding dithioacetates **7f**, **7g** and **7h**<sup>II</sup> (Scheme 10).



Scheme 10

Interestingly, N-phenyl-N-chloroacetyl ethyl glycinate resisted all attempts at bromination.<sup>II</sup>

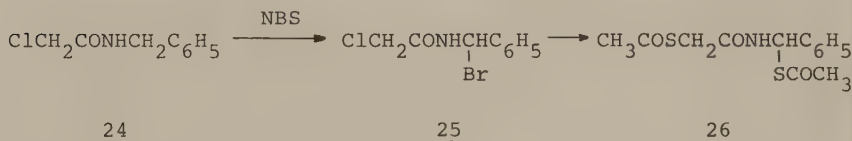
Bromination was found to be a convenient method of functionalization of the 2-position of chloroacetamido malonate 20.<sup>II</sup> The brominated compound 21 was treated in the usual way (cf. Scheme 4) with potassium thioacetate in methylene chloride to give the monosubstituted derivative 22 (Scheme 11). Unexpectedly, treatment of 22 in ethanol with a second equivalent of potassium thioacetate resulted in a return to the 2-unsubstituted amidomalonnate 23 (Scheme 11).<sup>II</sup>



Scheme 11

Evidently, the electron-deficient sulfur of 22 was the site of the nucleophilic attack by the thioacetate ion.<sup>II</sup>

NBS bromination was successful in functionalization the benzylic position of N-benzyl chloroacetamide (24). However, the crude dithioacetate 26 {NMR (DMSO-d<sub>6</sub>) δ 2.35 (s, 6H, CH<sub>3</sub>), 3.68 (s, 2H, CH<sub>2</sub>CO), 6.64 (d, 2H, J = 8.5 Hz, CHN), 7.35 (s, 5H, H<sub>arom</sub>), 9.30 (d, 1H, J = 8.5 Hz, NH)} obtained via the brominated product 25 analogously to 7g described in Ref. II was found to be unstable<sup>14</sup> (cf. 2.2.).



Scheme 12



3. 4-AZA-1,2-DITHIANE-5-ONES AND THE RELATED  
12-MEMBERED HETEROCYCLES

3.1. Synthesis

The following dithioacetates 7 were subjected to further conversions along the reaction path outlined in Scheme 2.

Table 1. Dithioacetates 7

$$\begin{array}{c} \text{R}_3 \quad \text{R}_1 \text{R}_2 \\ | \quad | \quad | \\ \text{CH}_3\text{COSCHCONCHSCOH}_3 \end{array}$$

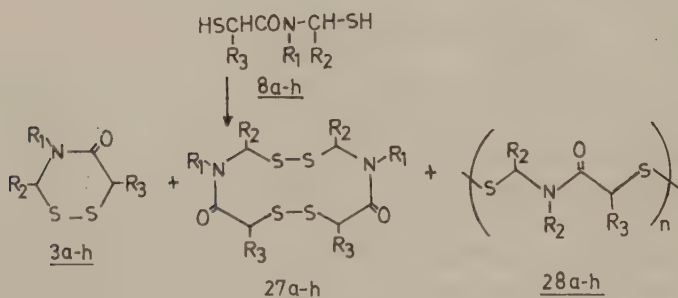
| <u>7</u> | R <sub>1</sub>                                | R <sub>2</sub>                                | R <sub>3</sub>                |
|----------|-----------------------------------------------|-----------------------------------------------|-------------------------------|
| <u>a</u> | H                                             | H                                             | H                             |
| <u>b</u> | (CH <sub>3</sub> ) <sub>2</sub> CH            | H                                             | CH <sub>3</sub>               |
| <u>c</u> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> | H                                             | H                             |
| <u>d</u> | C <sub>6</sub> H <sub>5</sub>                 | H                                             | H                             |
| <u>e</u> | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> | CONHC <sub>6</sub> H <sub>5</sub>             | H                             |
| <u>f</u> | CH <sub>3</sub>                               | CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> | H                             |
| <u>g</u> | H                                             | CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> | H                             |
| <u>h</u> | H                                             | CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> | C <sub>6</sub> H <sub>5</sub> |

3.1.1. Synthesis of N-thiomethyl-2-(thio)acetamides

Dithioacetates 7a-h were hydrolysed in 1.2 M methanolic or ethanolic hydrogen chloride to the corresponding N-thiomethyl-2-(thio)acetamides 8a-h. Three of them, 8a,<sup>III</sup> 8d<sup>V</sup> and 8g<sup>IV</sup> were characterized, whereas the others were used directly without purification.

### 3.1.2. Oxidations of N-thiomethyl-2-(thio)acetamides

Oxidations were carried out in chloroform using aqueous iodine/potassium iodide solution.<sup>IV,V</sup> This procedure, when applied to the dithiol 8b, gave a mixture of unidentified products, but oxidation of this dithiol with iron(III) chloride in ether gave a product suitable for characterization.<sup>V</sup> The dithiol 8d was also oxidized by carboethoxysulphenyl chloride.<sup>1</sup> Three different types of products were obtained on oxidation of dithiols 8a-h (Scheme 13), the proportions being dependent on the nature of the substrate<sup>IV,V</sup> (Table 2).



Scheme 13

Table 2. Oxidation of dithiols 8a-h<sup>a)</sup>

| Dithiol <u>8</u> | Products of oxidations     |                         |                   | Ref. |
|------------------|----------------------------|-------------------------|-------------------|------|
|                  | Yield <sup>d)</sup> (%) of |                         |                   |      |
|                  | Dithiane <u>3</u>          | Cyclododecane <u>27</u> | Polymer <u>28</u> |      |
| <u>a</u>         | 0                          | 89                      | 0                 | V    |
| <u>b</u> )       | 0                          | 0                       | 65                | V    |
| <u>c</u>         | 0                          | 0                       | 72                | V    |
| <u>d</u> )       | 25 <sup>e)</sup>           | 25                      | 50 <sup>e)</sup>  | V    |
| <u>e</u>         | 83                         | 0                       | 0                 | IV   |
| <u>f</u>         | 78                         | 0                       | 0                 | IV   |
| <u>g</u>         | 0                          | 81                      | 0                 | IV   |
| <u>h</u>         | 0                          | 67                      | 0                 | IV   |

a) aqueous iodine/potassium iodide was used unless otherwise specified

b) Fe(III)Cl<sub>3</sub>·6H<sub>2</sub>O in ether was used for oxidation of this compound

c) oxidation of this compound with carboethoxysulphenyl chloride gave a mixture whose NMR spectrum indicated a 50 % yield of 3d and a 50 % yield of 28d

d) yields of NMR pure products

e) yields calculated on the basis of rel. intensities of the appropriate signals in the NMR spectrum of the mixture of 3d and 28d

### 3.1.3. Structure determination of the so formed disulfides

Proof that the products of oxidation of dithiols 8e and 8f, were the desired dithianes, 3e and 3f, was obtained from analytical, NMR and mass spectral data. In addition, the molecular weight estimation carried out for compound 3e by the osmotic vapour pressure method gave a result close to that expected for a compound having this structure.<sup>IV</sup> An X-ray structure determination recently obtained for 3e<sup>17</sup> confirmed that this compound was 4-benzyl-3-phenylaminocarbonyl-4-aza-1,2-dithiane-5-one.

Oxidation of dithiol 8d gave a mixture of three components, of which only one was soluble in ether. One of the other two components was only sparingly soluble in chloroform.<sup>VI</sup> The evidence that this component was a dimer of the desired dithiane 3d was obtained from its mass spectrum, supported by analytical and NMR spectral data.<sup>V</sup> Interestingly, only one of the two possible dimeric isomers, 27d and 27'd, (Fig. 1) was formed. NMR and Raman spectral data implied that this product

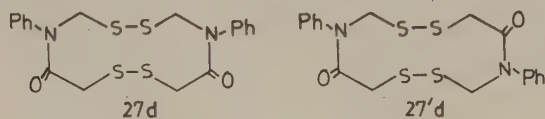


Fig 1

was 27d.<sup>VI</sup> The following observations led to this conclusion: (1) the down-field  $^1\text{H}$  NMR shift by 1.5 ppm of one isocronous couple of N-methylene protons ( $\text{H}_a$  in Figure 2), compared with the shift of the corresponding protons of 8d, implied a Z arrangement of the amide bonds and a coplanar position of these protons with the respective amide planes, pointing towards the carbonyl groups.<sup>30</sup>

(2) The Raman spectrum exhibited one band in the range  $450\text{--}600\text{ cm}^{-1}$  with a maximum at  $\sim 515\text{ cm}^{-1}$ , indicating that the dihedral angles of the disulfide bonds were not significantly distorted from the low energy value of  $\sim 90^\circ$ .<sup>31</sup> It was found by studying models of 27d and 27'd that in the conformation of 27'd for which conditions (1) and (2) were satisfied, one enantiotopic couple of  $\alpha$ -carbonyl protons ( $\text{H}_b$ ) would have been forced into regions of strong shielding of carbonyl functions. Yet, no upfield shift of these protons was observed in the NMR spectrum.<sup>VI</sup> Additionally, the activation barrier for inter-conversion between the conformers ( $\Delta G^\ddagger = 17.3 \pm 0.1\text{ kcal/mol}$ ) was in better agreement with structure 27d.<sup>VI</sup> It was therefore concluded<sup>VI</sup> that the dimeric product of the oxidation of 8d was 4,11-diphenyl-4,11-diaza-1,2,7,8-tetrathia-cyclododecane-5,10-dione (27d).

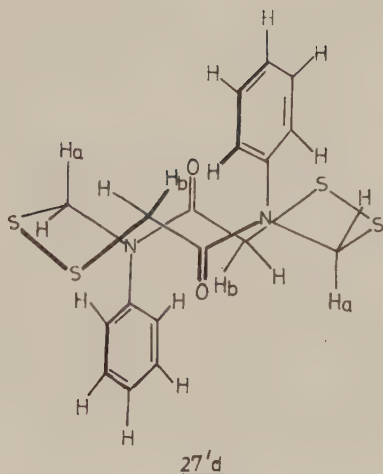
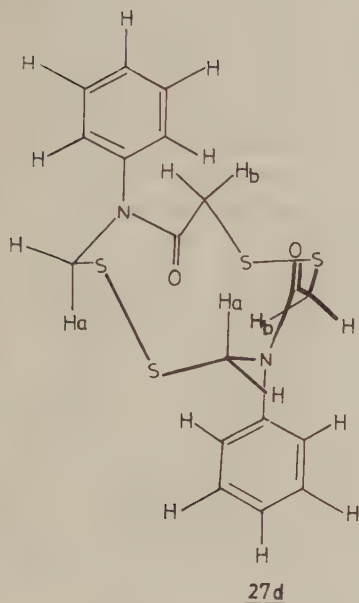


Fig 2

All analytical and spectral data obtained for the ether soluble component of the oxidation product of 8d indicated that this compound was the desired 4-phenyl-4-aza-1,2-dithiane-5-one (3d).<sup>V</sup> The third component of this product mixture was a rubbery material, for which the analytical and mass spectral data were in agreement with the structure of 3d. However, the <sup>1</sup>H NMR spectrum consisted of broad signals, indicating that this material was a polymeric form, 28d.<sup>V</sup> The neat dithiane 3d, although stable in solution, polymerized on standing. Conversely, the polymer 28d partially monomerized on heating in dimethyl sulfoxide.<sup>V</sup>

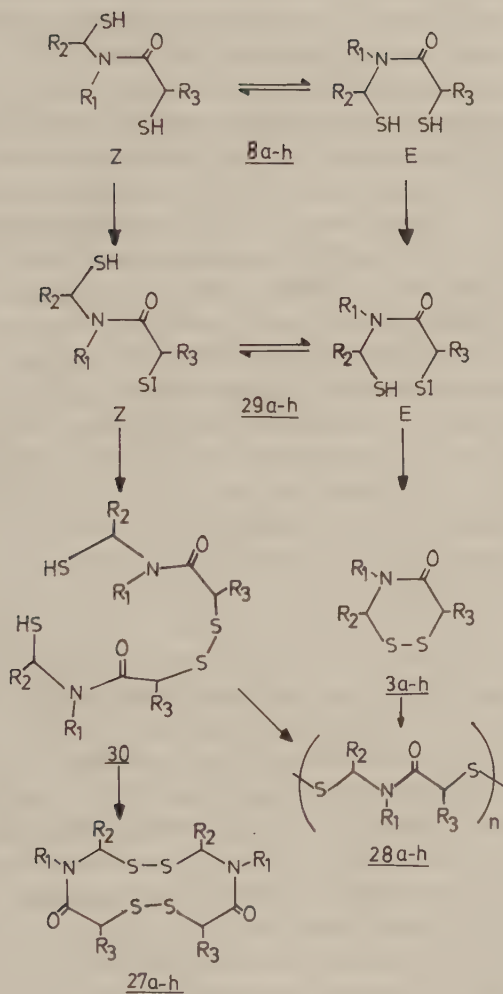
The oxidation products of dithiols 8b and 8c were rubbery materials, for which analytical and mass spectral data were in agreement with the structures of the desired dithianes 3b and 3c. However, the  $^1\text{H}$  NMR spectra consisted of broad signals, and the  $^{13}\text{C}$  NMR spectrum of the oxidation product of 8c exhibited over 100 peaks indicating that these materials (28b and 28c) were polymeric.<sup>V</sup> These polymers partially monomerized on heating in dimethyl sulfoxide- $\text{d}_6$ . Unfortunately, the resulting 3b and 3c monomers were too unstable to be isolated.<sup>V</sup>

Each of 8a,<sup>V</sup> 8g<sup>IV</sup> and 8h<sup>IV</sup> afforded, on oxidation, a single compound. According to the analytical, NMR and mass spectral data these compounds were dimers of the desired dithianes 3a, 3g and 3h.

Molecular weight estimation carried out by the osmotic vapour pressure method, of the oxidation product of 8h supported this assignment.<sup>IV</sup> Providing they were formed by the same mechanism as was 27d, these dimers should also be 4,11-diaza-1,2,7,8-tetrathia-cyclododecane-5,10-diones 27a,<sup>V</sup> 27g<sup>IV</sup> and 27h.<sup>IV</sup>

#### 3.1.4. Mechanism of oxidations

To rationalize the variety of products obtained on oxidation of 8a-h, a mechanism outlined in Scheme 14 was proposed.<sup>IV</sup> According to this mechanism, iodine preferentially attacks the  $\alpha$ -carbonyl thiol of 8a-h due to the higher nucleophilicity of this group compared to that at the other end of the molecule. The resulting sulfenyl iodide intermediates 29a-h exist in equilibrium of Z and E conformations of the amide bond. Since the monomeric cyclization can only take place in the E conformation of 29a-h, it must be favoured by low Z/E ratio. To be able to estimate these ratios, we made an assumption that they could be approximated by the Z/E ratios of the corresponding dithioacetates 7a-h.<sup>IV</sup> In this way, the Z/E ratios of the intermediates 29e and 29f, leading to the monomeric products, were estimated as being close to 6,<sup>IV</sup> while the Z/E ratios of 29a, 29d, 29g and 29h, leading to the predominantly dimeric or polymeric products, were estimated to be approximately 100 or



Scheme 14



more.<sup>IV,V</sup> The estimated Z/E ratios of 29b and 29c were less than 3 and these intermediates were therefore expected<sup>V</sup> to yield monomeric products. However, only polymeric materials were formed, which can be accounted for by the instability of the originally formed monomers.<sup>V</sup>

The proposed oxidation mechanism was supported by simple kinetic calculations<sup>IV</sup> based on the knowledge of the rotational energy barriers of 7e-g. Thus, it was shown that, due to the lower Z/E ratio, the monomeric cyclization of 29e and 29f was at least 20 times faster than the corresponding cyclization of 29g. It is therefore probable that the competing dimeric oxidation was slower than the monomeric cyclization in the case of 29e and 29f, but faster in the case of 29g.

The selective formation of dimers 27a, d, g and 27h could be the consequence of a regiospecific attack of the sulfenyl iodide moiety of the corresponding intermediates 29 on the more nucleophilic  $\alpha$ -carbonyl sulfur of the dithiols 8. This attack would result in the formation of symmetrically substituted disulfides 30 (Scheme 14) which, on further oxidation, would yield dimers 27.

### 3.2. Stability of the 4-aza-1,2-dithiane-5-one system

The 4-aza-1,2-dithiane-5-ones 3b-d all of which are unsubstituted in the 3-position, polymerize easily. The instability of cyclic disulfides is usually attributed to ring strain caused by distortion of the dihedral angle of the disulfide bond from the low-energy value of  $90^\circ$ .<sup>18</sup> Thus, 1,2-dithiolane adopting an angle of  $27^\circ$ ,<sup>19</sup> polymerizes easily<sup>18</sup> whereas 1,2-dithiane, having a  $60^\circ$  angle,<sup>20</sup> is indefinitely stable.<sup>18</sup> Unsaturation in 4,5 positions reduces the stability of the 1,2-dithiane system.<sup>18</sup> Conversely,  $\alpha$ -substitution of 1,2-dithiolane increases it,<sup>18</sup> probably by steric hindrance with regard to nucleophilic and electrophilic attack on the sulfur atoms, which often initiate polymerization.<sup>18</sup>

The distortion of the dihedral angle is related to both the polarographic behaviour<sup>22</sup> and the position of the long-wave

UV absorption of the disulfide chromophore.<sup>21</sup> According to UV spectroscopic and polarographic studies performed on 3e and 3f, the 4-aza-1,2-dithiane-5-one system should be free from substantial ring strain.<sup>V</sup> This was confirmed by the recently obtained X-ray spectroscopic data, showing that the dihedral angle adopted by the disulfide bond of 3f was 60.4° and thus not significantly distorted.<sup>17</sup> The degree of instability of cyclic disulfides is usually paralleled by a similar degree of reactivity towards cyanide ion.<sup>18</sup> Thus, 1,2-dithiolane rapidly undergoes ring-opening on reaction with cyanide, whereas 1,2-dithiane resists attack by this nucleophile.<sup>18</sup> Indeed, since cyanide is too weak a nucleophile to displace a thiolate anion from alkyl disulfides, special conditions, such as ring strain, electron withdrawal or subsequent reactions of the products on the right hand side of the equation below, are necessary to effect such a displacement.<sup>23</sup>

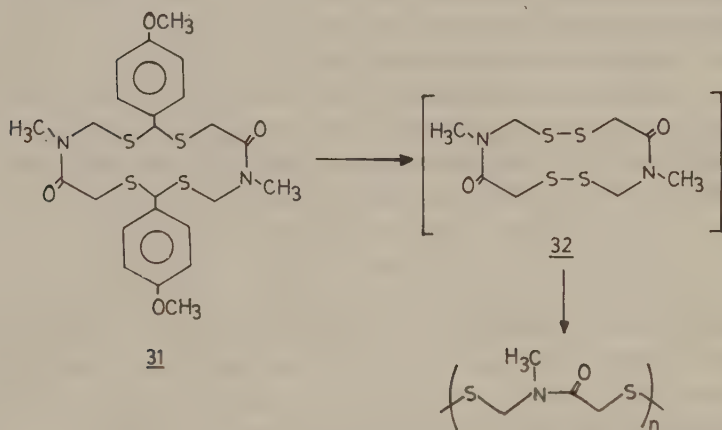


The dithiane 3e, although free from substantial ring strain, reacts rapidly with cyanide ion.<sup>V</sup> This shows that this system is sensitive to nucleophilic attack, possibly because of the electron withdrawal from the sulfur atoms.

Unsymmetrical disulfides having electron-deficient sulfur atoms are known to undergo disproportionation catalyzed by nucleophiles,<sup>24</sup> electrophiles,<sup>25</sup> heat or even ambient light.<sup>26</sup> Since the stable dithianes 3e and 3f both carry a substituent at the 3-position of the ring, protecting the 2-sulfur atom against nucleophilic attack, the instability of the 3-unsubstituted derivatives 3b-d could be due to the lack of such protection. Disproportionation, leading to polymerization, might be initiated by the amide function of the 4-aza-1,2-dithiane-5-one ring. This function is known to effect disproportionation in other systems.<sup>24</sup>

### 3.3. Stability of 12-membered rings related to 4-aza-1,2-dithiane-5-ones

An attempt to prepare N,N'-dimethyl-4,10-diaza-1,2,7,8-tetra-thia-cyclododecane-5,11-dione (32) from the dithioacetal 31<sup>III</sup> by Kishi's procedure<sup>2</sup> was not successful, only polymeric materials being obtained.<sup>V</sup>



Scheme 15

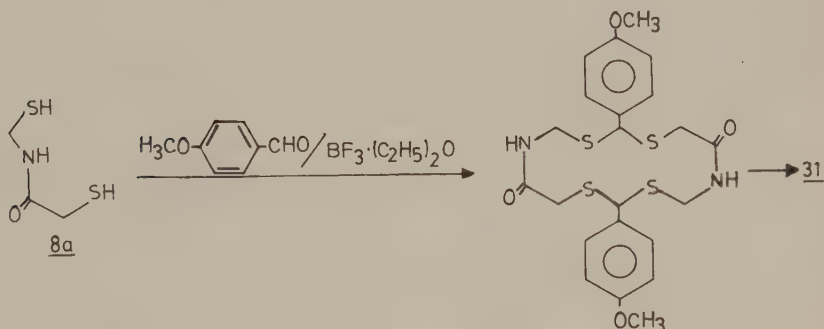
A model of the N,N'-diphenyl derivative 27'd (Fig. 2) showed that, to adopt a conformation where the dihedral angles of the disulfide bonds were close to the low-energy value of 90° and the amide bonds had the low-energy Z disposition, the planes of the amide bonds would have to lie in close proximity.<sup>VI</sup> Strong interactions between protons pointing towards the centre of the ring and the amide functions, as well as between the phenyl rings and the sulfur atoms or N-methylene protons, would then be inevitable. Conformations containing distorted disulfide bonds or amide groups having an E arrangement would also be energetically unfavoured.<sup>1,32</sup> These results indicate

that the 4,10-diaza-1,2,7,8-tetrathia-cyclododecane-5,11-dione structure might not be stable.

N,N'-Diphenyl-4,11-diaza-1,2,7,8-tetrathia-cyclododecane-5,10-dione (27d) is a stable compound.<sup>V</sup> Similarly, the other 12-membered heterocycles obtained on oxidation of the dithiols 8a,g,h (presumably 27a,b,h) were found to be indefinitely stable. IV,V

4. REGIOSPECIFIC REACTION OF ANISALDEHYDE WITH  
N-THIOMETHYL-THIOGLYCOLIC ACID AMIDE

The dithiol 8a was reacted with anisaldehyde in the presence of boron trifluoride etherate in an attempt to protect the thiol functions,<sup>III</sup> as in the method of Kishi et al.<sup>2</sup> The product was then converted to an N-methyl derivative which, by X-ray analysis, was shown to be 2,9-bis(p-methoxyphenyl)-5,12-dimethyl-5,12-diaza-1,3,8,10-tetrathiacyclotetradecane-6,13-dione (31).<sup>III</sup>



Scheme 16

Interestingly, only one of two possible dimeric isomers was obtained and this was attributed<sup>III</sup> to the dimerization of the intermediate 33 (Fig. 3), formed on reaction of the more

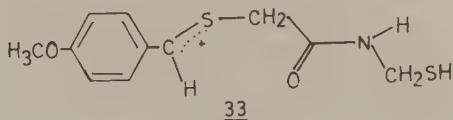
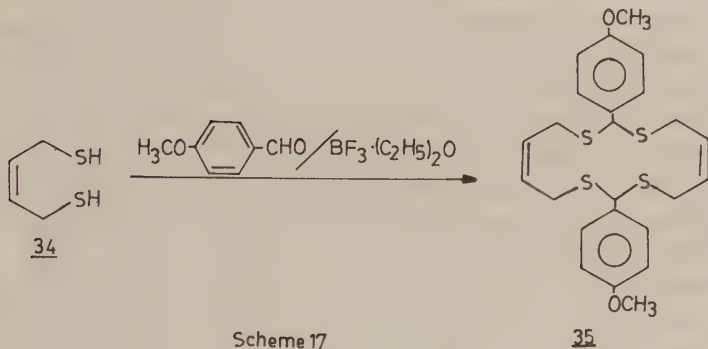


Fig 3

nucleophilic  $\alpha$ -carbonyl SH group with the active anisaldehyde - boron trifluoride complex. The higher nucleophilicity of the  $\alpha$ -carbonyl thiol function of 8a became evident from the reaction of this dithiol with acetyl chloride. This reaction showed that the preferred site of the electrophilic attack by acetyl chloride was the  $\alpha$ -carbonyl sulfur.<sup>III</sup>

Formation of isomeric or polymeric products on reaction of aldehydes with dithiols in acidic media has been previously reported<sup>27</sup> and the success of the monothioacetalization of Kishi's dithiols (3,6-dithio-piperazinediones) seems quite exceptional. In order to find out if this was due to cis-arrangement in these dithiols, cis-1,4-dithio-2-butene (34)<sup>28</sup> was reacted with anisaldehyde in the presence of boron trifluoride etherate. The product was again a dimeric compound 35 (Scheme 17), showing that a cis-arrangement of the thiol functions is not a sufficient condition for monothioacetalization.<sup>III</sup>



Scheme 17

5. ANTIVIRAL ACTIVITY OF 3-AZA-1,2-DITHIANE-5-ONES  
AND CONCLUSIONS

The dithianes 3e and 3f show no antiviral activity. This indicates that the epidithiopiperazinedione structure is probably the smallest part of gliotoxin (1a), and the related natural products responsible for inhibition of viral RNA polymerase.

This investigation also shows, that the difference in nucleophilicity of the SH groups of unsymmetrical dithiols could have interesting synthetic implications.

ACKNOWLEDGEMENTS

I acknowledge with deep gratitude the confidence which Professor Salo Gronowitz has shown by leaving this project in my hands and the help he gave me. I also wish to thank Dr. Tommy Liljefors and Professor Jan Sandström for their encouragement, constant interest and valuable advice during this investigation. Thanks are due to Dr. Ulf Berg, Messrs. Zoltan Blum and Roland Isaksson for teaching me new techniques, to Mr. Jan Glans for recording UV and most of the  $^1\text{H}$  NMR spectra, to Messrs. Rolf Servin and Einar Nilsson for recording  $^1\text{H}$  NMR and mass spectra, to Mrs. Ann Moberg-Ogard for drawing the figures and Mrs. Ann Nordlund for typing. I am also much obliged to Messrs. Lars Trege and Ove Anderberg for help with the technical problems and to Drs. Robert Carter and Andrew Webber for the linguistic criticism, which often expanded into valuable criticism of the very content. Furthermore, I would like to thank all my friends at the Department of Organic Chemistry for their valuable advice and stimulating discussions.

This work was supported by grants from the Faculty of Science at the University of Lund and the Royal Physiographic Society in Lund.



## REFERENCES

1. L. Field in S. Oae's "Organic Chemistry of Sulfur", p. 303.  
Plenum Press, New York and London 1977
2. Y. Kishi, T. Kugugama and S. Nakatsuka,  
J. Am. Chem. Soc. 95, 6490 (1973)
3. S.G. Svokos, N.J. Westwood and R. Bruce,  
US Patent 3,560,483 (1971)
4. P.W. Trown, Biochem. Res. 33, 402 (1968)
5. H.C. Ottenheijm, T.F. Spande and B. Witkop,  
J. Am. Chem. Soc. 95, 1989 (1973)
6. H.C. Ottenheijm, N.E. Vermeulen and L.F.J.M. Breuer,  
Liebigs Ann. Chem. 206 (1974)
7. H.E. Zaugg and W.B. Martin, Org. React. 14, 52 (1965)
8. M. Pranka and D.J. Polton, British Patent 917,924 (1963)  
Chem. Abstr. 58, 1488a (1963)
9. H. Böhme, A. Dick and G. Driesen,  
Chem. Ber. 94, 1879 (1961)
10. J. Graymore, J. Chem. Soc. 1353 (1932)
11. a) J.P. Chupp, J.F. Olin and H.K. Landwehr,  
J. Org. Chem. 34, 1192 (1969); b) K.W. Ratts and J.P. Chupp,  
J. Org. Chem. 39, 3745 (1974)
12. H. Böhme and K. Hartke, Chem. Ber. 96, 600 (1963)
13. a) H. Leuchs and A. Schlotzer,  
Ber. Dtsch. Chem. Ges. 67, 1572 (1934)  
b) H. Poisel and U. Schmidt, Chem. Ber. 108, 2917 (1975)  
c) F.W. Fowler and A. Hassner,  
J. Am. Chem. Soc. 90, 2875 (1968)
14. Z. Lidert, unpublished results
15. a) R.K. Olsen and A.J. Kolar,  
Tetrahedron Letters 41, 3579 (1975)  
b) P.M. Pojer and I.D. Rae, Aust. J. Chem. 25, 1737 (1972)
16. H. Poisel and U. Schmidt, Chem. Ber. 108, 2547 (1975)
17. I. Cynkier, to be published
18. A. Schöberl and H. Fräffje, Liebigs Ann. Chem. 614, 66 (1958)
19. G. Bergson, Arkiv Kemi 22, 265 (1962)

20. O. Foss and T. Reistad,  
Acta Chem. Scand. 11, 1427 (1957)
21. G. Bergson, "Some New Aspects of Organic Disulfides,  
Diselenides and Related Compounds",  
Almqvist and Wiksell, Stockholm 1962
22. B. Nygård, Arkiv Kemi 28, 75 (1967)
23. A.J. Parker and N. Kharasch, Chem. Rev. 59, 583 (1959)
24. a) L. Field, W.S. Hanley and I. McVeigh,  
J. Org. Chem. 36, 2735 (1971)  
b) A. Schöberl and H. Fräffe,  
Liebigs Ann. Chem. 617, 71 (1958)  
c) M. Bellas, D.L. Tuleen and L. Field,  
J. Org. Chem. 32, 2591 (1967)
25. K. Ikura and S. Oae, Tetrahedron Lett. 3791 (1968).
26. L. Field, T.F. Parsons and D.E. Pearson,  
J. Org. Chem. 31, 3550 (1966)
27. C.S. Marvel, E.A. Sienicki, M. Passer and C.N. Robinson,  
J. Am. Chem. Soc. 76, 933 (1954)
28. A. Lüttringhaus, S. Kabuss, W. Mair and H. Friebohn,  
Z. Naturforsch. 16, 761 (1961)
29. a) F. Sachs and R. Kempf, Chem. Ber. 35, 1235 (1902)  
b) C.O. Cech, *ibid.* 11, 248 (1878)
30. U. Berg, M. Grimaud and J. Sandström,  
Nouveau J. Chim. 3, 175 (1979)
31. H.E. Wart and H.A. Scheraga, J. Phys. Chem. 80, 1823 (1976)
32. H. Kessler and A. Rieker, Liebigs Ann. Chem. 708, 57 (1967)







